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Heart and Vessels

ISSN 0910-8327

Heart Vessels
DOI 10.1007/s00380-015-0716-7

Springer

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DOI 10.1007/s00380-015-0716-7

ORIGINAL ARTICLE

Association between smoking habits and severity of coronary stenosis as assessed by coronary computed tomography angiography

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Received: 9 March 2015 / Accepted: 10 July 2015

Abstract Smoking promotes arteriosclerosis and is one of the most important coronary risk factors. However, few studies have investigated the association between smoking habits and the severity of coronary stenosis as assessed by coronary computed tomography angiography (CTA). We enrolled 416 patients [165/251 = smoker (past and current)/non-smoker)]. They had all undergone CTA and either were clinically suspected of having coronary artery disease (CAD) or had at least one cardiovascular risk factor. We divided the patients into smoking and non-smoking groups, and evaluated the presence of CAD, the number of significantly stenosed coronary vessels (VD), and the Gensini score as assessed by CTA in the two groups. The incidence of CAD, VD, the Gensini score, and coronary calcification score in the smoking group were all significantly greater than those in the non-smoking group (CAD, $p = 0.009$; VD, $p = 0.003$; Gensini score, $p = 0.007$; coronary calcification score, $p = 0.01$). Pack-year was significantly associated with VD and the Gensini score, and was strongly associated with multi-vessel disease (2- and 3-VD) ($p < 0.05$), whereas the duration of cessation in past smokers was not associated with VD or the Gensini score. Pack-year, but not the duration of cessation, may be the most important factor that was associated with the severity of coronary stenosis in terms of VD and the Gensini score.

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Keywords Smoking habits · Coronary computed tomography angiography · Coronary artery disease · Gensini score

Introduction

Smoking is a risk factor for various diseases such as malignant tumor and respiratory illness, and is one of the most important coronary risk factors [1–5]. Some studies have reported that the amount of cigarette smoking is related to coronary arteriosclerosis [6–9] and is associated with an increased risk of the onset of coronary artery disease (CAD) [10–13]. Therefore, smoking cessation is being actively promoted worldwide. However, the incidence of smokers in Japan as of 2012 is still 20.7 %, which is higher than in many other countries [14]. Thus, we believe that it is important to study the relationship between smoking and the severity of coronary arteriosclerosis in the Japanese population. Coronary computed tomography angiography (CTA) has become more widely available in many general hospitals and emerged as a potential non-invasive method for predicting CAD. Few studies have investigated the association between smoking habits and the severity of coronary atherosclerosis as assessed by CTA in Japan. One study investigated the relationship between the amount of cigarette smoking and coronary arteriosclerosis by CTA in asymptomatic individuals [9]. They reported a cigarette dose–response relationship between current smoking and coronary arteriosclerosis in asymptomatic individuals. However, this report did not include symptomatic individuals or those who were clinically suspected of having CAD. Furthermore, the relationship between the duration of cessation and the severity of coronary arteriosclerosis was unknown. We hypothesized that the duration of cessation

Published online: 18 July 2015

in addition to the amount of cigarette smoking could be associated with the severity of coronary arteriosclerosis. Therefore, we enrolled patients who had undergone CTA and who either were clinically suspected of having CAD or had at least one cardiovascular risk factor, and investigated the association between smoking habits (amount of cigarette smoking and duration of cessation) and the severity of coronary stenosis as assessed by CTA.

Methods

Subjects

We enrolled a total of 416 consecutive patients who underwent CTA from April 2012 to June 2014 and were clinically suspected of having CAD based on abnormal findings by electrocardiography and/or chest symptoms (such as chest pain or chest discomfort) or had at least one cardiovascular risk factor [smoking, abdominal obesity, dyslipidemia (DL), hypertension (HTN), and/or diabetes mellitus (DM)]. Patients in whom we could not evaluate coronary stenosis due to severe calcification, or who had acute coronary syndrome, Kawasaki disease or Marfan syndrome, were excluded. The protocol in this study was approved by the ethics committee of Fukuoka University Hospital [IRB #11-06(09-089)], and all subjects gave their written informed consent to participate.

Evaluation of coronary stenosis using CTA

We evaluated coronary stenosis using multi detector-row computed tomography (MDCT) as previously described [15]. Three hundred seventeen patients who had undergone MDCT from April 2012 to January 2014 were scanned by 64-MDCT on an Aquilion 64 (TOSHIBA, Tokyo, Japan), and 99 patients who had undergone MDCT from February 2014 to June 2014 were scanned by 320-MDCT on an Aquilion ONE ViSION (TOSHIBA, Tokyo, Japan). All segments were assessed according to the 15-segment American Heart Association (AHA) coronary artery model [16]. Any narrowing of the normal contrast-enhanced lumen on coronary artery $\geq$50 % that could be identified in multiple reconstructions or cross-sectional images was analyzed. Lumen diameter stenosis $\geq$50 % was defined as significant coronary stenosis.

Evaluation of patient characteristics including biochemical parameters

Data regarding age, gender, body mass index (BMI), smoking status (current and past smoker and non-smoker), medication use, systolic blood pressure (SBP), diastolic BP (DBP), heart rate (HR), left ventricular ejection fraction (LVEF), serum levels of triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), uric acid (UA), hemoglobin A1c (HbA1c) and random plasma glucose (BS), estimated glomerular filtration rate (eGFR), high sensitivity C reactive protein (hs-CRP), and pentraxin-3 (PTX-3) were collected in all patients. The number of pack-years was calculated as [packs (where 1 pack consists of 20 cigarettes) smoked per day $\times$ years as a smoker]. BP was determined as the mean of two measurements obtained in an office setting by the conventional cuff method using a mercury sphygmomanometer after at least 5 min of rest. The characteristics of the patients with regard to history of HTN, DL, and DM were obtained from medical records. Patients who had a current SBP $\geq$140 mmHg and/or DBP $\geq$90 mmHg or who were receiving antihypertensive therapy were considered to have HTN. Patients with LDL-C $\geq$140 mg/dl, TG $\geq$150 mg/dl, and/or HDL-C <40 mg/dl, or who were receiving lipid-lowering therapy were considered to have DL. Patients with random BG $\geq$200 mg, fasting BG $\geq$126 mg, and/or HbA1c $\geq$6.5 %, or who were taking a glucose-lowering drug were considered to have DM. Hyperuricemia (HU) was defined as a serum UA level of $\geq$7.0 mg/dl or the administration of uric acid-lowering drugs. In all subjects, we also measured the visceral fat area (VFA) and subcutaneous fat area (SFA) as assessed by CT, and waist circumference (WC) as components of metabolic syndrome (MetS). Chronic kidney disease (CKD) was defined as an eGFR level <60 ml/min/1.73 m^2.

Statistical analysis

Statistical analysis was performed using the Stat View statistical software package (Stat View 5; SAS Institute Inc., Cary, NC, USA). Data are expressed as the mean $\pm$ standard deviation (SD). The significance of differences was evaluated using the unpaired and paired t test for continuous variables and the χ^2 test for non-continuous variables. Since the variables of number of significant stenosed coronary vessels (VD), coronary calcification score, and Gensini score (Table 3) did not show a normal distribution expressed as a median value and interquartile range, we performed a Mann–Whitney U test. The Spearman Rank Correlation Coefficient was used to evaluate associations between the groups. We used a multiple logistic regression analysis for the multivariate analysis to evaluate independent predictors for multivessel disease and selected age ($\geq$65 years), gender, BMI (>25 kg/m^2), HTN, DM, and DL in addition to pack-year as independent variables. A receiver operating characteristic (ROC) curve analysis was used to determine the cut-off values of pack-year for distinguishing between no- or 1-VD and multi-vessel disease at the highest possible sensitivity and specificity. A value of $p < 0.05$ was considered significant.

Results

Patient characteristics including biochemical parameters

Tables 1 and 2 show the patient characteristics in all patients and the smoking and non-smoking groups. The smoking group showed significantly higher percentages of males and DM, and higher levels of DBP, VFA, TG, BS, HbA1c, and UA, and significantly lower levels of SFA, LDL-C, and HDL-C than the non-smoking group. Table 3 shows the severity of coronary arteriosclerosis [percentage of CAD, VD, percentage of multi-vessel disease (2- and 3-VD), calcification score and Gensini score] in the smoking and non-smoking groups. The smoking group showed significantly higher percentages of CAD, multi-vessel disease, a higher Gensini score, and a higher coronary calcification score than those in the non-smoking group (CAD, $p = 0.009$; multi-vessel disease, $p = 0.0004$; Gensini score, $p = 0.007$; coronary calcification score, $p = 0.01$).

Table 1 Patient characteristics in all patients and the smoking and non-smoking groups

	All ($n = 416$)	Smoking ($n = 165$)	Non-smoking ($n = 251$)
Age (years)	65.4 ± 12.1	64.0 ± 11.3	66.3 ± 12.5
Male, *n* (%)	215 (51.6)	138 (64)*	77 (36)
BMI (kg/m^2)	23.9 ± 3.6	24.3 ± 3.6	23.7 ± 3.5
HTN, *n* (%)	294 (70.6)	124 (75.1)	170 (67.7)
DL, *n* (%)	271 (65.4)	111 (67.2)	160 (64.2)
DM, *n* (%)	95 (22.8)	51 (30)*	44 (17.5)
HU, *n* (%)	57(13.8)	28 (17)	29 (11.9)
CKD, *n* (%)	59 (14.1)	20 (12.1)	39 (15.5)
Medication			
ARB, *n* (%)	158 (38)	64 (39)	94 (37)
ACE-I, *n* (%)	12 (2.8)	6 (3.6)	6 (2.3)
β-blocker, *n* (%)	45 (10)	20 (12)	25 (9)
CCB, *n* (%)	150 (36)	56 (34)	94 (37)
Diuretic, *n* (%)	42 (10)	16 (8)	26 (10)
Statin, *n* (%)	142 (34)	53 (32)	89 (35)
EPA, *n* (%)	10 (2)	4 (2)	6 (2)
SU, *n* (%)	30 (7)	17 (10)	13 (5)
Biguanide, *n* (%)	29 (6)	16 (9)	13 (5)
DPP4-I, *n* (%)	44 (10)	22 (13)	22 (8)

BMI body mass index, *HTN* hypertension, *DL* dyslipidemia, *DM* diabetes mellitus, *HU* hyperuricemia, *CKD* chronic kidney disease, *ARB* angiotensin II receptor blocker, *ACE-I* angiotensin-converting enzyme inhibitor, *CCB* calcium channel blocker, *EPA* eicosapentaenoic acid, *SU* sulfonylurea and *DPP4-I* dipeptidyl peptidase-4 inhibitor

* $p < 0.05$ vs. non-smoking

Association between smoking habits and inflammatory markers (hs-CRP and PTX-3)

We also investigated the association between smoking habits and inflammatory markers (hs-CRP and PTX-3) (Fig. 1). The current smoker group showed significantly lower levels of PTX-3 than the past smoker ($p = 0.008$), never smoker ($p = 0.03$), and never smoker + past smoker ($p = 0.012$) groups (Fig. 1a), whereas there were no significant differences in the levels of hs-CRP among groups (Fig. 1b). Pack-year was not significantly correlated with hs-CRP or PTX-3 (data not shown).

Association between pack-year or cessation and severity of coronary stenosis

We investigated the association between smoking habits (pack-year and duration of cessation) and the severity of coronary stenosis in the smoking group. Pack-year and duration of cessation were 40 (20–60) packs × years and 4 (0–14) years, respectively. Pack-year and the Gensini score showed a weak positive correlation ($r = 0.193$, $p = 0.013$), whereas the duration of cessation in past smokers was not significantly correlated with the Gensini score ($p = 0.944$) (Fig. 2). In addition, pack-year was significantly associated with VD (p for trend 0.008) and multi-vessel disease ($p < 0.05$) (Fig. 3a, b), whereas the duration of cessation in past smokers was not associated with VD or multi-vessel disease (Fig. 3c, d). Furthermore, we divided past smokers into short duration of cessation (<10 years) and long duration of cessation (<20 years) groups. There were no significant differences in the severity of coronary stenosis between the groups (data not shown). We also investigated the association between duration of cessation and the severity of coronary stenosis in the smoking group (current and past smokers). The duration of cessation in the smoking group was not associated with VD or multi-vessel disease (data not shown).

Predictors of multi-vessel disease in all patients

Next, we analyzed the predictors of multi-vessel disease in all patients using independent variables by a logistic regression analysis (Table 4). We selected pack-year in addition to conventional coronary risk factors [age (≥65 years), gender (male), BMI (≥25 kg/m^2), HTN, DL, and DM] as independent variables. HTN ($p = 0.0003$), DL ($p = 0.027$), DM ($p = 0.008$), gender ($p = 0.0005$), age ($p = 0.025$), and pack-year (OR 1.01, $p = 0.037$) were identified as

Table 2 Various hemodynamic and biochemical parameters in all patients and the smoking and non-smoking groups

	All	Smoking	Non-smoking
SBP (mmHg)	137 ± 20	137.4 ± 17.1	135.5 ± 19.6
DBP (mmHg)	79.2 ± 12.8	79.2 ± 12.8*	75.6 ± 12.4
HR (min^{-1})	75 ± 12	72.8 ± 13.5	74.7 ± 13.1
LVEF (%)	70 ± 11	68.3 ± 9.7	69.7 ± 9.9
WC (cm)	84 ± 10	88 ± 9	86 ± 9
SFA (cm^2)	138 ± 78	134 ± 67*	165 ± 7
VFA (cm^2)	99 ± 62	128 ± 64*	105 ± 51
eGFR (ml/min)	72 ± 24	68 ± 16	68 ± 19
TG (mg/dl)	138 ± 84	156 ± 107*	124 ± 63
LDL-C (mg/dl)	113 ± 33	108 ± 29*	115 ± 32
HDL-C (mg/dl)	52 ± 13	51 ± 15*	56 ± 15
BS (mg/dl)	112 ± 38	114 ± 32*	106 ± 28
HbA1c (%)	6.0 ± 0.7	6.1 ± 1.0*	5.9 ± 0.9
UA (mg/dl)	5.4 ± 1.2	5.7 ± 1.2*	5.1 ± 1.2

SBP systolic blood pressure, *DBP* diastolic BP, *HR* heart rate, *LVEF* left ventricular ejection fraction, *WC* waist circumference, *VFA* visceral fat area, *SFA* subcutaneous fat area, *eGFR* estimated glomerular filtration rate, *TG* triglyceride, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *BS* fasting blood glucose, *HbA1c* hemoglobin A1c and *UA* uric acid

* $p < 0.05$ vs. non-smoking group

significant independent variables that predicted multi-vessel disease.

We also defined the cut-off value of pack-year for multi-vessel disease. The cut-off level for pack-year with the greatest sensitivity and specificity for the presence of multi-vessel disease was 26.25 (sensitivity 0.438, specificity 0.841) by ROC curve analysis. Finally, we divided the patients in the smoking group into heavy pack-year ≥26.25) and light smokers (pack-year <26.25) using this cut-off value for pack-year. Multi-vessel disease was strongly and independently associated with pack-year ($p = 0.009$) in addition to HTN and DL (Table 5).

Discussion

We demonstrated that smoking habits were significantly associated with the severity of coronary stenosis as assessed by CTA. The most important finding in this study was that the amount of cigarette smoking (pack-year), but not the duration of cessation, was the most important factor associated with the severity of coronary stenosis. Next, multi-vessel disease was independently associated with pack-year in addition to HTN, DL, DM, age and gender.

Table 3 Assessment of severity of coronary atherosclerosis in the smoking and non-smoking groups

	Smoking	Non-smoking	*p* value smoking vs. non-smoking
CAD (%)	101 (61)	121 (48)	0.009
VD (vessels)	1 (0–2)	0 (0–1)	0.003
Multi-vessel disease (%)	69 (42)	62 (25)	0.0004
Coronary calcification score	27.7 (0–213.4)	2.78 (0–123.1)	0.01
Gensini score	11.5 (4–18.5)	6.25 (1.5–15.4)	0.007

CAD coronary artery disease, *VD* the number of significant stenosed coronary vessels

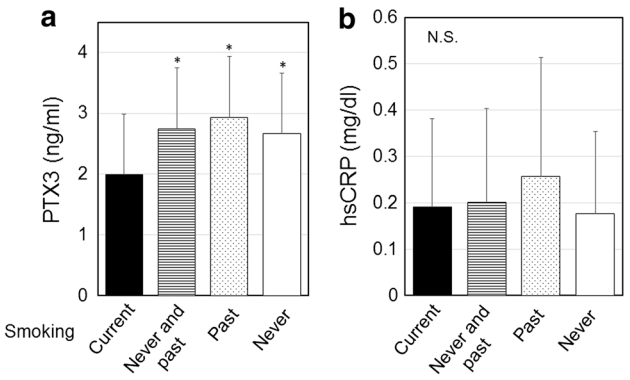

Fig. 1 Associations between smoking habits and inflammatory markers [PTX-3 (**a**) and hs-CRP (**b**)]. *N.S.* not significant. *$p < 0.05$ vs. current smoker

Many studies have shown that the amount of cigarette smoking is associated with vascular disease. Although current smoking of >20 cigarettes/day increased the risk of CAD among middle-aged hypertensive men in a prospective study in Japan [17], the total amount of cigarette smoking in their life was unknown. Therefore, in this study, we replaced the amount of cigarette smoking with pack-year and investigated the association between the dose–response of smoking and the severity of coronary arteriosclerosis. One study investigated the relationship between the amount of cigarette smoking and coronary atherosclerosis by coronary CTA in asymptomatic individuals [9]. The results showed that the prevalence of coronary arteriosclerosis in current smokers of more than 20 pack-years was significantly higher than that

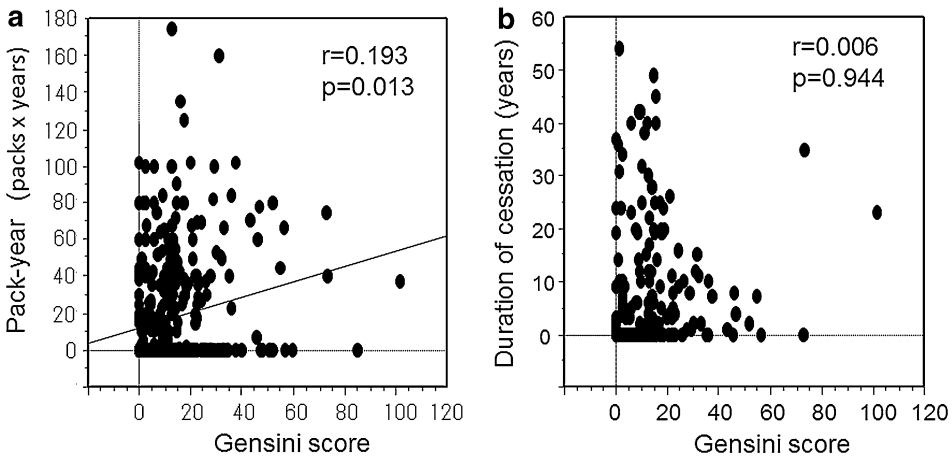

Fig. 2 Association between pack-year (**a**) or duration of cessation (**b**) and the Gensini score

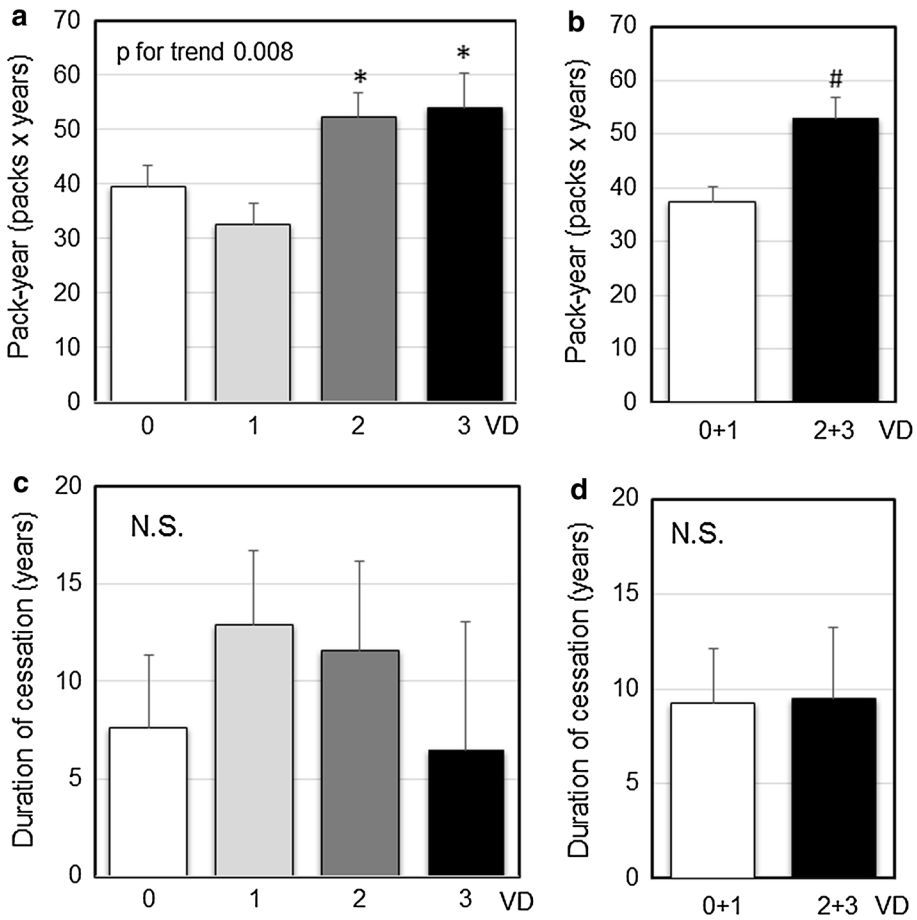

Fig. 3 Association between pack-year (**a**, **b**) or duration of cessation (**c**, **d**) and the severity of coronary stenosis [the number of significantly stenosed coronary vessels (VD) and multi-vessel disease (2 + 3 VD)]. *N.S.* not significant. $^{*}p < 0.05$ vs. 0 V. $^{\#}p < 0.05$ vs. 0 + 1 VD

in never smokers. In this study, we investigated another very important factor: the association between the duration of cessation and coronary arteriosclerosis. Our study showed that the duration of cessation in past smokers was not associated with the severity of coronary arteriosclerosis. Some studies have reported that smoking cessation is associated with a decrease in the onset rate of CAD [18–22]. A case–control study in Italy showed that there was a substantial drop in the risk of acute myocardial infarction 1 year after cessation [23]. In addition, although several similar reports stated that smoking cessation reduced the risk of CAD [24, 25], these studies did not investigate the association between pack-year and CAD. Furthermore, these studies investigated the association between smoking habits and MI or mortality, rather than the severity of coronary arteriosclerosis. Our study does not conflict with

Table 4 Predictors of multi-vessel disease in all patients

	Odds ratio	95 % CI	*p* value
Age ≥65	1.77	1.076–2.914	0.025
Gender (male)	2.58	1.511–4.413	0.0005
BMI ≥25	0.80	0.496–1.342	0.410
HTN	2.94	1.627–5.305	0.0003
DL	1.78	1.669–2.969	0.027
DM	2.03	1.207–3.418	0.008
Pack-year	1.01	1.001–1.018	0.037

CI confidence interval, *BMI* body mass index, *HTN* hypertension, *DL* dyslipidemia, *DM* diabetes mellitus

Table 5 Predictors of multi-vessel disease in the smoking group

	Odds ratio	95 % CI	*p* value
Age (≥65)	1.83	0.868–3.853	0.113
Gender (male)	3.00	0.954–9.452	0.603
BMI (≥25)	1.10	0.505–2.409	0.806
HTN	3.08	1.259–7.526	0.014
DL	2.25	1.029–4.932	0.042
DM	1.27	0.591–2.730	0.543
Pack-year (≥26.25)	3.03	1.319–6.967	0.009

CI confidence interval, *BMI* body mass index, *HTN* hypertension, *DL* dyslipidemia, *DM* diabetes mellitus

these previous reports, since the outcome of our study was the presence or absence of coronary plaque. For example, current smokers are more likely to have lipid-rich plaque and OCT-defined vulnerable plaque, while former smokers have more calcified plaque [26], and these results may explain the increased risk of acute cardiac events among smokers. Although we did not evaluate the quality of plaque in our subjects, plaque may be stabilized by the improvement of inflammation in blood vessels that results from smoking cessation. In this study, we were not able to find an association between smoking cessation and the severity of coronary arteriosclerosis. Therefore, smoking cessation can stabilize the plaque and may decrease coronary events, although smoking cessation dose not regress coronary arteriosclerosis.

Low-grade inflammation may exist in smokers and inflammation in blood vessels may be improved by smoking cessation [27, 28]. CRP has been suggested to be a marker of cardiovascular disease risk [29–32]. Several studies have reported a positive association between smoking and CRP levels [33–37]. Many prospective epidemiologic studies have demonstrated that hs-CRP independently predicts vascular risk. Furthermore, it has been reported that PTX-3 is associated with cardiovascular risk factors [38]. In our study, we investigated the association between smoking habits and inflammatory markers (hs-CRP and PTX-3). The current smoking group showed significantly lower levels of PTX-3, whereas there were no significant differences in the level of hs-CRP, and pack-year was not significantly correlated with hs-CRP or PTX-3 (data not shown). Thus, current smoking is important for its effect on the levels of PTX-3. Since PTX-3 may have an atheroprotective role in addition to serving as a marker of inflammation [39], smoking might downregulate the levels of PTX-3. Further detailed analysis will be needed to resolve this issue.

This study has several important limitations. First, the study was cross-sectional and included a relatively small number of patients. Second, the severity of coronary atherosclerosis by CTA was evaluated after various treatments. Third, CTA is not a gold standard for the evaluation of CAD, although recent studies have shown that both its sensitivity and specificity were approximately 95 % of those for invasive coronary angiography for the identification of significant coronary stenosis. Fourth, there was a small number of current smokers ($n = 56$, 13.4 %).

In conclusion, pack-year, but not the duration of cessation, was shown to be the most important factor that is associated with the severity of coronary stenosis in terms of VD and the Gensini score.

Compliance with ethical standards

Conflict of interest K. S. is a Chief Director and S. M. is a Director of NPO Clinical and Applied Science, Fukuoka, Japan. K. S. has an Endowed "Department of Molecular Cardiovascular Therapeutics" supported by MSD, Co. LTD. S. M. belongs to the Department of Molecular Cardiovascular Therapeutics, which is supported by MSD, Co. LTD.

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